REMARKS

Claims 5, 7 and 34-56[1] were pending in this application. In order to expedite the prosecution of the present application and without conceding to the validity of the Examiner's rejections, Applicants have canceled claims 5, 7, 34 and 35, without prejudice to Applicants' right to pursue the subject matter of the canceled claims in related applications. Applicants have amended claims 36-39 and 46 to more particularly point out and distinctly claim the invention. In particular, claims 36 and 37 have been amended to clarify that if, for example, position 4 of the cyclopentenone ring has an aliphatic side chain, then position 5 of the cyclopentenone ring would not have an aliphatic side chain, and *vise versa*. Claims 38 and 39 have been amended to clarify that the cyclopentenone ring lacks an aliphatic side chain at both the 4 and 5 positions. Claim 46 has been amended to delete the redundancy of the term "virus." A marked up version of the amended claims showing the amendments made herein, with additions indicated by underlining and deletions indicated by brackets, is attached hereto as Exhibit A. The amendments to the claims are fully supported by the specification, see, *e.g.*, pages 11-12 of the specification of the present application, and do not constitute new subject matter. Claims 36-56 will therefore be pending upon entry of this Amendment. A copy of the claims which will pending upon entry of this Amendment is attached hereto as Exhibit A.

The amendments and remarks made herein narrow the issues on appeal and are designed to place the case in condition for allowance. As such, Applicants respectfully request that the amendments and remarks made herein be entered and fully considered.

1. CLAIMS 41-53 SHOULD BE CONSIDERED

Claims 41-53 have been withdrawn from consideration as being directed to a non-elected invention. In particular, the Examiner contends that the elected invention is directed to cytoprotective uses, not disease therapy. Applicants respectfully disagree with the Examiner's withdrawal of claims 41-53 from examination. Contrary to the Examiner's contention, claims 41-53 are ***not*** directed to a non-elected invention, namely disease therapy. Rather, dependent claims 41-53 define the human subject that achieves the cytoprotective responses following the administration of the compounds recited in independent claims 36-39. Accordingly, Applicants respectfully request that dependent claims 41-53 be considered and examined in the present application.

[1] The Examiner incorrectly states on page 2 of Paper No. 13 that claim 57 is presented for examination. As of Paper No. 13, there was no claim 57 presented for examination.

2. THE REJECTIONS UNDER 35 U.S.C. § 102(b) SHOULD BE WITHDRAWN

Claims 5, 7, 36 and 38 are rejected under 35 U.S.C. § 102(b) as being anticipated by Amici *et al.*, 1993, Experimental Cell Research 207:230-234 (hereinafter "Amici"), Del Soldato, 1981, Boll. Chim. Farm. 120:631-638 (hereinafter "Del Soldato"), or European Patent Application No. EP 0 106 576 to Noyori *et al* (hereinafter "Noyori"). The Examiner contends that Amici, Del Soldato and Noyori each inherently anticipate the invention recited in claims 5, 7, 36 and 38. For the reasons detailed below, Applicants respectfully assert that the rejections under 35 U.S.C. § 102(b) cannot stand and should be withdrawn.

It is axiomatic that for a prior art reference to anticipate a claimed invention under 35 U.S.C. § 102(b), it has to meet every element of the claimed invention. *Hybritech Inc. v. Monoclonal Antibodies, Inc.* 802 F.2d 1367, 231 U.S.P.Q. 81, 91 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987).

In order to expedite prosecution of the present application and without conceding to the validity of the Examiner's rejections, Applicants have canceled claims 5 and 7, without prejudice, and amended claims 36 and 38. Amended claim 36 recites a method of inducing cytoprotective responses in a human subject by administering a therapeutically effective amount of a compound that induces the expression of heat shock proteins, which compound has a cyclopentenone ring structure and an aliphatic side chain at position 4 or 5 and lacking an aliphatic chain at the position 4 or 5 not containing the aliphatic side chain. Amended claim 38 recites a method of inducing cytoprotective responses in a human subject by administering a therapeutically effective amount of a compound that induces the expression of one or more heat shock proteins, which compound has a cyclopentenone ring structure which lacks an aliphatic side chain at positions 4 and 5.

None of the cited reference disclose methods of inducing cytoprotective responses in a human subject by administering a therapeutically effective amount of a compound that induces the expression of heat shock proteins, which compound has a cyclopentenone ring structure which lacks an aliphatic side chain at position 4 and/or 5 as recited in claims 36 and 38.

Amici describes the induction of a thermotolerant state in the cell line K562 by the natural prostaglandin PGA_1. PGA_1 is structurally different from the compounds recited in claims 36 and 38. PGA_1 has long aliphatic side chains at positions 4 ***and*** 5. In contrast, the compounds recited in claims 36 and 38 lack an aliphatic side chain at positions 4 and/or 5.

Thus, the compounds that Amici uses to induce the thermotolerant state in the K562 cell line are distinct from the compounds recited in claims 36 and 38. Moreover, Amici does ***not*** describe the administration of PGA_1 to a human subject, must less the administration of the compounds recited in claims 36 and 38 to a human subject. Accordingly, Amici does not describe the compounds recited in claims 36 and 38, much less the methods recited in claims 36 and 38, and therefore, does not anticipate claims 36 and 38.

Del Soldato describes the cytoprotective properties of PGE_2, a cyclo***pentan***one prostaglandin, in an experimental rat model. PGE_2 is structurally different from the compounds recited in claims 36 and 38. Unlike the compounds recited in claims 36 and 38, PGE_2 does not contain a carbon-carbon double bond in its ring structure. Moreover, Del Soldato does not describe the administration of PGE_2 to a human subject, much less the administration of the compounds recited in claims 36 and 38 to a human subject. Accordingly, Del Soldato does not describe the compounds recited in claims 36 and 38, much less the methods recited in claims 36 and 38, and therefore, does not anticipate claims 36 and 38.

Noyori primarily describes the synthesis of cyclopentenone prostaglandin-like compounds having two adjacent aliphatic side chains. Noyori alleges that such compounds may be useful as anti-tumor agents. Noyori does ***not*** describe a cyclopentenone compound having an aliphatic side chain at position 4 or 5 and lacking an aliphatic chain at the position 4 or 5 not containing the aliphatic side chain as required by claim 36. Further, Noyori does not describe a cyclopentenone compound lacking an aliphatic side chain at position 4 and 5 as required by claim 38. Rather, the compounds described by Noyori require an aliphatic side chain at positions 4 ***and*** 5.

Noyori does ***not*** describe administering any compounds to a ***human*** subject, much less the compounds recited in claims 36 and 38. The only disclosure in Noyori regarding the administration of compounds is ***generic*** (*i.e.*, refers generically to a subject) or refers to ***non-human cells and/or mice*** (see Noyori at pages 22-24 and pages 55-60). For example, Noyori in examples 35 and 36 reports that an anti-tumor effect was observed in a murine leukemia cell line and mice when cyclopentenone compounds with aliphatic side chains at the 4 ***and*** 5 positions were administered. In example 37, the only example pertaining to cytotoxicity and the only mention of cytotoxicity in Noyori, Noyori reports that a difference in the cytotoxicity of cyclopentenone compounds with aliphatic side chains at the 4 ***and*** 5 positions was observed when these compounds were added to rabbit stomach epithelial cells and rat fetus and aortic smooth muscle cells relative to a murine leukemia cell line. Given that there

are differences between mice, rabbits and rats, the experiment described in example 37 does not provide the appropriate controls, and thus, does ***not*** provide the basis for making any conclusions regarding the cytotoxicity of compounds. Accordingly, Noyori does not describe methods of inducing cytoprotective responses in a ***human*** subject by administering a cyclopentenenone compound recited in claim 36 or 38.

Therefore, neither Amici, Del Soldato nor Noyori meet each and every element of the presently claimed invention, and therefore, do not anticipate claims 36 and 38. Accordingly, Applicants respectfully assert that the rejection under 35 U.S.C. § 102(b) cannot stand and should be withdrawn.

3. THE REJECTIONS UNDER 35 U.S.C. § 103(a) SHOULD BE WITHDRAWN

Claims 5, 7 and 34-56[2] are rejected under 35 U.S.C. § 103 as being unpatentable over Amici, Noyori and Del Soldato. The Examiner contends that Amici, Del Soldata and Noyori "teach the claimed compounds as old and well known in combination with various pharmaceutical carriers and excipients in a dosage form. These medicaments are taught as useful for providing cytoprotection, viewed by the skilled artisan as indistinguishable for those uses herein claimed." For the reasons detailed below, Applicants respectfully disagree and submit that the rejections under 35 U.S.C. § 103 cannot stand and should be withdrawn.

A finding of obviousness requires a determination of the scope and content of the prior art, the level of ordinary skill in the art, the differences between the claimed subject matter and the prior art, and whether the differences are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere* 383 U.S. 1 (1996). The proper inquiry is whether the art suggests the invention, and whether the art provides one of ordinary skill in the art with a reasonable expectation of success. *In re O'Farrell* 853 F.2d 894, 7 U.S.P.Q. 2d 1673 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art and not in the Appellants' disclosure. *In re Vaeck* 947 F.2d 488, 20 U.S.P.Q. 2d 1438 (Fed. Cir. 1991).

In order to expedite prosecution of the present application and without conceding to the validity of the Examiner's rejections, Applicants have canceled claims 5, 7, 34 and 35, without prejudice, and amended claims 36-39. Amended claim 36 recites a method of

[2] The Examiner incorrectly states that claims 5, 7 and 34-57 are rejected under 35 U.S.C. § 103 on page 4 of Paper No. 13. As of Paper No. 13, there was and still is no pending claim 57; only claims 5, 7 and 34-56 were pending as of Paper No. 13. Accordingly, Applicants assume that the Examiner meant to state that claims 5, 7 and 34-56 are rejected under 35 U.S.C. § 103 on page 4 of Paper No. 13.

inducing cytoprotective responses in a human subject by administering a therapeutically effective amount of a compound that induces the expression of heat shock proteins, which compound has a cyclopentenone ring structure and an aliphatic side chain at position 4 or 5 and lacking an aliphatic chain at the position 4 or 5 not containing the aliphatic side chain. Amended claim 37 recites a method of inducing both cytoprotective and NF-κB inhibitory activities in a human by administering to a human a therapeutically effective amount of a compound that induces the expression of one or more heat shock proteins and downregulates or inhibits NF-κB activity, which compound has a cyclopentenone ring structure and has an aliphatic side chain at position 4 or 5 and lacks an aliphatic side chain at the position 4 or 5 not containing the aliphatic chain. Amended claim 38 recites a method of inducing cytoprotective responses in a human subject by administering a therapeutically effective amount of a compound that induces the expression of one or more heat shock proteins, which compound has a cyclopentenone ring structure that lacks an aliphatic side chain at positions 4 and 5. Amended claim 39 recites a method of inducing both cytoprotective and NF-κB inhibitory activities in a human subject by administering a therapeutically effective amount of a compound that induces the expression of one or more heat shock proteins and downregulates or inhibits NF-κB activity, which compound has a cyclopentenone ring structure that lacks an aliphatic side chain at positions 4 and 5.

None of the cited references, alone or in combination, teach or suggest the methods of the presently claimed invention. As discussed above, Amici[3] reports the induction of a thermotolerant state in the cell line K562 by the natural prostaglandin PGA_1. Amici does ***not*** teach or suggest cyclopentenone compounds that lack an aliphatic side chain at positions 4 and/or 5 as recited in independent claims 36-39. Rather, Amici describes a natural cyclopentenone prostaglandin which has long fatty acid side chains at positions 4 ***and*** 5, which are not encompassed by the presently claimed invention. Moreover, Amici does ***not*** teach the administration of any cyclopentenone compounds to a ***human*** subject, much less the administration of the cyclopentenone compounds recited in independent claims 36-39. Accordingly, Amici does not render the claimed invention obvious.

Del Soldato describes the cytoprotective properties of a cyclop***entan***one prostaglandin, namely PGE_2, in an experimental rat model. In other words, Del Soldato describes the cytoprotective properties of a prostaglandin that lacks an α,β-unsaturated double bond in its ring structure. Del Soldato does ***not*** teach or suggest cyclopentenone compounds that lack an aliphatic side chain at positions 4 and/or 5 as recited in independent claims 36-

[3] A publication by the co-inventors of the present application.

39. Moreover, Del Soldato does ***not*** describe the administration of PGE_2 to a ***human*** subject, much less the compounds recited in claims 36 and 38 to a human subject. Accordingly, Del Soldato does not render the claimed invention obvious.

The deficiencies in Amici and Del Soldato are not cured by Noyori. Noyori focuses on the synthesis of cyclopentenone prostaglandin-like compounds having two adjacent aliphatic side chains. Noyori does not describe a cyclopentenone compound having an aliphatic side chain at position 4 or 5 and lacking an aliphatic chain at the position 4 or 5 not containing the aliphatic side chain as required by claim 36 and 37. Further, Noyori does not describe a cyclopentenone compound lacking an aliphatic side chain at position 4 and 5 as required by claim 38 and 39. Rather, the compounds described by Noyori require an aliphatic side chain at positions 4 ***and*** 5. Thus, unlike the presently claimed invention, Noyori requires substitution at both the 4 ***and*** 5 positions of the cyclopentenone ring.

Noyori does ***not*** describe or suggest administering any compounds to a ***human*** subject, much less the compounds recited in independent claims 36-39. Rather, Noyori only ***generically*** describes administering a compound to a subject, without specifying the species of the subject, or to ***non-human cells and/or mice*** (see Noyori at pages 22-24 and pages 55-60). For example, Noyori in the example section only reports the results from experiments conducted on a murine leukemia cell line or mice when cyclopentenone compounds with aliphatic side chains at the 4 ***and*** 5 positions were administered. Accordingly, Noyori does not describe methods of inducing cytoprotective responses in a ***human*** subject by administering a cyclopentenenone compound as required by the presently pending claims.

Moreover, Noyori only suggests the use of compounds as anti-tumor agents and mentions in passing the use of compounds as anti-viral agents. Noyori does ***not*** teach or suggest inducing one or more heat shock proteins, inducing NF-κB inhibitory activity or inducing a cytoprotective effect. There is only one instance where Noyori mentions cytoprotection and that is in the title of example 37; Noyori entitles example 37 "Measurement of cyto protection." In example 37, Noyori reports that a difference in the cytotoxicity of cyclopentenone compounds with aliphatic side chains at the 4 ***and*** 5 positions was observed when these compounds were added to rabbit stomach epithelial cells and rat fetus and aortic smooth muscle cells relative to a murine leukemia cell line. Given that there are differences between mice, rabbits and rats, the experiment described in example 37 does not provide the appropriate controls, and thus, does ***not*** provide the basis for making any conclusions regarding the cytotoxicity of compounds, much less the cytoprotective properties of such compounds. Accordingly, Noyori does not teach or suggest the use of cyclopentenone compounds with aliphatic side chains at the 4 ***and*** 5 positions to induce a

cytoprotective effect in a ***human*** subject, much less the use of cytoprotective compounds lacking an aliphatic side chain at positions 4 and/or 5 to induce a cytoprotective effect in a human subject. Therefore, Noyori, alone or in combination, does not render the presently claimed invention obvious.

In view of the foregoing, Applicants respectfully assert that the rejections under 35 , U.S.C. § 103(a) cannot stand and should be withdrawn.

CONCLUSION

Applicants respectfully request entry and consideration of the foregoing amendments and remarks. Applicants believe that all of the present claims meet all of the requirements for patentability. Withdrawal of all rejections is requested.

If any issues remain, the Examiner is requested to telephone the undersigned at (212) 790-6293.

Respectfully submitted,

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EXHIBIT A

A MARKED UP VERSION OF THE CLAIMS AMENDED

IN THE AMENDMENT FILED MAY 1, 2003

IN U.S. APPLICATION SERIAL NO.: 09/533,339

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36. (amended) A method of inducing cytoprotective responses in a human, comprising administering to a human in which such treatment is desired a therapeutically effective amount of a compound, which compound induces the expression of one or more heat shock proteins, wherein the compound has a cyclopentenone ring structure [which lacks a long aliphatic side chain at position 4 or 5] and has an aliphatic side chain at position 4 or 5 and lacks an aliphatic side chain at the position 4 or 5 not containing the aliphatic chain.

37. (amended) A method of inducing both cytoprotective and NF-κB inhibitory activities in a human, comprising administering to a human in which such treatment is desired a therapeutically effective amount of a compound, which compound induces the expression of one or more heat shock proteins and downregulates or inhibits NF-κB activity, wherein the compound has a cyclopentenone ring structure [which lacks a long aliphatic side chain at position 4 or 5] and has an aliphatic side chain at position 4 or 5 and lacks an aliphatic side chain at the position 4 or 5 not containing the aliphatic chain.

38. (amended) A method of inducing cytoprotective responses in a human, comprising administering to a human in which such treatment is desired a therapeutically effective amount of a compound, which compound induces the expression of one or more heat shock proteins, wherein the compound has a cyclopentenone ring structure which lacks [a long] an aliphatic side chain at positions 4 and 5.

39. (amended) A method of inducing both cytoprotective and NF-κB inhibitory activities in a human, comprising administering to a human in which such treatment is desired a therapeutically effective amount of a compound, which compound induces the expression of one or more heat shock proteins and downregulates or inhibits NF-κB activity, wherein the compound has a cyclopentenone ring structure which lacks [a long] an aliphatic side chain at positions 4 and 5.

49. (amended) The method of claim 46, wherein the paramyxovirus is morbillivirus [virus] or pneumovirus.